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By Deanna L. Miller
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:
**Dwayne Thomas Friesen, et al.**

Examiner: **T. Ware**

APPLICATION NO.: **09/380,825**

FILING DATE: **September 7, 1999**

Group Art Unit: **1615**

TITLE: **Solubilized Sertraline Compositions**

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE UNDER RULE 1.121

Responsive to the Office Action of January 29, 2003 reconsideration and reexamination of this application are requested in view of the following comments which are made at this time in order to place this application in condition for allowance or in better form for appeal, should the finality of the Office Action be maintained.

This application relates to a composition comprising sertraline or a pharmaceutically acceptable salt thereof and a solubilizing agent that prevents gel formation or otherwise maintains the solubility of sertraline in a use environment containing chloride ions.

Claims 1-32 have been rejected under 35 USC 102(b) as being anticipated by Welch, Jr. et al., U.S. 4,536,518 (hereinafter referred to as "Welch Jr. et al"). The rejection is respectfully traversed.

It is well settled that in order to sustain a finding of anticipation, all material elements of a claim must be found in one prior art source, In re Marshall, 198 USPQ 344 (Fed.Cir. 1978); In re Kalm, 154 USPQ 10 (CCPA 1967), which must be enabling to one

skilled in the art. Akzo v. U.S. International Trade Commission, 1 USPQ2d 1241 (Fed.Cir.1986), i.e. enable that person to understand the nature and operation of the invention.

Claims 1-32 are clearly distinguished from Welch Jr. et al. The claims require the combination of sertraline in the form of a highly soluble salt form and a solubilizer present in a sufficient amount to increase the dissolved sertraline concentration in a use environment. There is no discussion in Welch Jr. et al. of highly soluble salt forms of sertraline. Welch Jr. et al. describe generally a very broad class of active compounds, of which sertraline is a single species. The discussion of salt forms in Welch Jr. et al. is limited to diastereomeric salt forms used to resolve racemic mixtures (column 6, lines 17-24), and a general discussion of acid addition salts. See column 6, lines 25-34. The only forms of sertraline described by Welch Jr. et al., are the free acid and hydrogen chloride salt form. The hydrochloride salt form has a solubility of about 2.5 mg/mL. (See patent application, page 15, line 9.) Thus, contrary to the Examiner's allegations, Welch Jr. et al. do not disclose the presently claimed highly soluble salt forms of sertraline.

Additionally, Welch et al. are silent on the use of a combination of a highly soluble salt form and a solubilizers. Welch Jr. et al. list several classes of specific compounds that may be included as excipients in tablets (Col. 7, lines 22-56). However, nowhere do Welch Jr. et al., describe the particular combination of a highly soluble salt form of sertraline and a solubilizing agent in a sufficient amount to increase the concentration dissolved sertraline in a use environment.

In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990) states that under 35 USC 102(b), every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim. As has been shown above, the statutory mandate for a finding of anticipation has not been met in the present case; withdrawal of the rejection under 35 USC 102(b) is requested.

Claims 1-67 have been rejected under 35 USC 103(a) as being obvious in view of Welch Jr. et al. The Examiner's comments have been carefully considered and the rejection is respectfully traversed.

The claims are patentably distinguished over Welch Jr. et al. for the reasons described above. In addition,it is respectfully pointed out that the present invention lies in

the recognition by the inventors herein that the solubility of sertraline was reduced in a chloride-ion containing environment. See page 5, lines 17-19 of the present specification. It was not previously recognized that a chemical agent existed that could reduce or prevent sertraline gelation. Applicants solved the problem of reduced solubility of highly soluble salts forms of sertraline in chloride-ion containing use environments by including a sufficient amount of a solubilizer. In this case, the invention lies in the discovery of the source of the problem (reduced solubility of sertraline in a chloride-ion containing use environment) and the recognition of a remedy. '[A] patentable invention may lie in the discovery of the course of a problem even though the remedy may be obvious once the source of the problem is identified; this is part of "subject matter as a whole" which should always be considered in determining obviusness of an invention under section 103' In re Sponnoble, 160 USPQ 237 (CCPA 1969), MPEP 2141.02. Welch Jr. et al., do not disclose the invention as a whole because Welch Jr. et al., do not recognize the problem of sertraline gelation in the presence of chloride ions nor do they teach or suggest the addition of a solubilizer to prevent or reduce gelation.

At page 3 of the Office Action the Examiner states: "'518 does not specifically teach inclusion of an organic acid as a solubilizer in the taught embodiments, however, '518 does teach inclusion of salts that dissolve in solution to form organic acids (e.g. sodium citrate) as excipients (i.e. fillers or carriers)." At page 4 the Examiner states "Applicant admits recognition that '518 teaches organic acids salts such as sodium citrate and argues that since these salts lack acidic functionality, they would not be expected to provide as much concentration enhancement as that provided by the organic acids."

The salts of organic acids described by Welch Jr. et al. are not as preferred as organic acids because some of such salts will not solubilize sertraline at all, while others will not improve solubility as much as the corresponding organic acid. For example, magnesium stearate, a lubricant described by Welch Jr. et al., is hydrophobic and does not meet the aqueous solubility requirement. Magnesium stearate is practically water insoluble having an aqueous solubility of less than 0.1 mg/ml. Similarly, calcium carbonate is also practically water insoluble, having an aqueous solubility of less than 0.1 μg/ml.

Organic acids are preferred over calcium carbonate and organic acids salts such as sodium citrate. This is because the acidic nature of organic acids allows the organic acids to react with sertraline to form salts having improved solubility relative to sertraline hydrochloride. Since organic acid salts by themselves lack acidic functionality, they would

not be expected to provide as much concentration enhancement as that provided by the organic acids.

Moreover, Welch Jr. et al., is silent with respect to the problem solved by Applicants' herein, namely the solubilization of sertraline. There is no teaching or suggestion in Welch Jr. et al., that the solubility of sertraline may be enhanced by organic acids.

Applicants respectfully direct the Examiner's attention to the attached table, which sets forth solubility analysis of the hydrochloride salt of sertraline. The table was used as the basis for the Table 1-1 presented in Example 1 of the instant specification. The attached table illustrates that organic acids have the ability to raise the solubility of the hydrochloride salt of sertraline. As stated in Example 1 of the instant specification, the acids were tested by dissolving the candidate acid in water and then stirring excess sertraline hydrochloride in the acid solution for at least 8 hours. The concentration of sertraline in the supernatant was then measured by HPLC analysis.

As examples, consider the data presented for citric acid, erythorbic acid and adipic acid. When one compares the solubility information from Column 1 with the solubility information from Column 4, it can be seen that the solubility of sertraline was successfully raised. Further, the data for sodium citrate shows the excipient does not provide as much concentration enhancement as that provided by the organic acids.

The data fully support Applicants' claims.

Moreover, the Examiner's comments with respect to claims 22-29 is not understood since the claims do recite sertraline is in the form of a highly soluble salt form. Clarification is requested.

A finding of unobviousness must be based on a comparison of the claimed invention with the teachings of the prior art. Graham v. John Deere, 148 USPQ 459 (Fed. Cir. 1966). It is not Applicants' burden to refute the Examiner's position that it would have been obvious to one of ordinary skill in the art at the time their invention was made to arrive at their invention in view of '518 (Welch Jr. et. al.). Applicants have clearly distinguished the present invention from Welch Jr. et. al. and have shown that such reference does not suggest the resolution of the problem of reduced solubility of

sertraline in a chloride-ion containing use environment. Accordingly, withdrawal of the rejection under 35 USC 103 is requested.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§ 1.16 and 1.17, or to credit any overpayment to Deposit Account No. 16-1445.

Respectfully submitted,

Date: 7/29/03

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| Excipient | Estimated excip. H2O sol. mg/ml | pH sat. excip. soln. | pH sat. w/ drug | drug sol. mgs/ml | Comments |
|---|---|---|---|---|---|
| Potassium sorbate | 580 | 10.7 | 8.1 | 84 | |
| g-cyclodextrin | 360 | 5.6 | 3.4 | 29 | |
| Trans-aconitic acid | 200 | 0.9 | 1.4 | 25 | Excipient soln. not saturated |
| D,L- Malic acid | >1300 | 0.1 | 1.0 | 21 | Excipient soln. not saturated |
| Citric acid | 600 | 0.4 | 1.3 | 20 | |
| Erythorbic acid | 400 | 2.2 | 1.7 | 19 | |
| Adipic acid | 14 | 2.7 | 2.3 | 12 | |
| b-cyclodextrin | 35 | 6.1 | 2.5 | 8.0 | |
| PEG 3350 NF | 50* | 6.2 | 2.9 | ~ 8.0 | |
| a-cyclodextrin | 50* | 4.4 | 2.7 | 6.5 | Excipient soln. not saturated |
| Maleic acid | >700 | 0.1 | 1.6 | 6.4 | Excipient soln. not saturated |
| L- Aspartic acid | 7 | 2.1 | 1.4 | 5.5 | |
| Tartaric acid | 1400 | 0.1 | 0.1 | 5.5 | |
| L-Glutamic acid | 12 | 2.3 | 1.7 | 5.4 | |
| Calcium gluconate | <33 | 6.9 | 6.1 | 3.1 | |
| Fumaric acid | 11 | 1.1 | 1.1 | 3.1 | |
| Ca phosphate (dibas) | <1 | 7.0 | 5.6 | 3.0 | |
| Pluronic F-38 | 50* | 7.1 | 4.0 | 3.0 | |
| Tannic acid | 3000 | 1.7 | 0.7 | 2.8 | Excipient soln. not saturated |
| D,L- Tyrosine | 600 | 6.9 | 6.2 | 2.2 | |
| Calcium sorbate | <1 | 6.5 | 6.2 | 1.9 | |
| SLS | 50* | 7.9 | 7.6 | 1.2 | Excipient soln. not saturated |
| Sodium citrate | 520 | 2.9 | 2.8 | 0.6 | |
| Calcium Fumerate | 3 | 4.1 | 4.2 | 0.4 | |
| K phosphate (mono) | 400 | 3.7 | 3.3 | 0.4 | |
| Sodium carbonate | 12 | 11 | 11 | < 0.1 | |
| L-lysine | >1000 | 10 | 10 | < 0.1 | |
| L-Arginine | 150 | 11 | 10 | < 0.1 | |

* Concentration used to measure solubility